REMARKS

Upon entry of the amendments made herein, claims 1, 4, 6-7, 9-11, 13, 14, 19, 21, 23-26, 30, 32, 34-40, 56-65, 67, 68, 82, 103-112, 117-143, 145-147 and 149-158 are pending in this application with claims 14, 25, 26, 30, 31, 33-40, 56-68 104-108, 111, 112, 117-143, 145-147 and 149-158 currently withdrawn from consideration. Claims 1, 4, 19, 30, 34, 63, 67 and 82 are currently amended. Claims 2, 3, 12, 31, 33 and 66 have been canceled herein without prejudice or disclaimer while claims 5, 8, 15-18, 20, 22, 27-29, 41-55, 69-81, 83-102, 113-116, 144 and 148 were previously canceled.

Claims 1 and 82 were amended to further define the invention. Support for the amendments can be found, *e.g.*, on page 6, lines 23-24 and on page 7, lines 11-12 of the specification as filed. Claims 4, 19, 30, 34, 63 and 67 were amended to maintain proper claim dependency or to maintain proper antecedent basis. Accordingly, no new matter has been added.

Formal Matters

According to the Examiner, because no generic claims were found patentable, the claims remain restricted in scope to the elected species only. Thus, the Examiner concluded that claims 14, 25, 26, 30, 31, 33-40, 56-68, 104-112, 117-139, 140-153 and 154-158 are withdrawn from consideration as drawn to unelected species. (*See* Office Action at p. 2). Applicants believe claims 109 and 110 are drawn to the elected species and request that they no longer be considered withdrawn.

Double Patenting

Claims 1-4, 6, 7, 9-14, 19, 21, 23, 24, 30-40, 82, 140-143 and 145-154 remain provisionally rejected under obviousness-type double patenting as being unpatentable over claims 1 and 26-54 of co-pending Application No. 10/839,023.

Applicants have canceled claims 2, 3, 12, 31 and 33 and claim 148 was previously canceled. Therefore, with respect to these claims, the rejection is moot.

With respect to claims 1, 4, 6, 7, 9-11, 13, 14, 19, 21, 23, 24, 30, 32, 34-40, 82, 140-143, 145-147 and 149-154, Applicants traverse the rejection and note that this rejection is a provisional double patenting rejection for which the M.P.E.P. at § 804 section I, subsection B1 provides as follows:

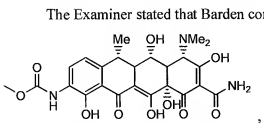
> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn.

The instant application claims priority as a continuation application to U.S. Application No. 09/823,884 (now U.S. Patent No. 6,818,634), filed on March 30, 2001. The cited co-pending Application No. 10/839,023 claims priority as a divisional application to U.S. Application No. 09/895,857 (now U.S. Patent No. 6,846,939), filed on June 29, 2001. Thus, the instant application is the earlier-filed application with respect to co-pending Application No. 10/839,023. Accordingly, should the Examiner find the present claims allowable in view of the arguments included herein, Applicants respectfully request withdrawal of the provisional double patenting rejection.

35 U.S.C. §103

Claims 1, 7, 11, 18, 23-25, 66 and 67 are rejected under 35 U.S.C. §103(a) as being unpatentable over Barden *et al.* (J. Med. Chem., 1994, v.37, no.20, p. 3205-3211) ("Barden") in view of Silverman, R. B. (The Org. Chem. Of Drug Design and Drug Action, Academic Press, Inc., SanDiego, 1992, p. 4-51) ("Silverman").

The Examiner stated that Barden compound 12,



, has greater activity in some respects than other compounds described therein and, thus, one of ordinary skill would have had sufficient

motivation to select compound 12 for further modification. (*See* Office Action at p. 3). Furthermore, the Examiner asserted that Barden provides motivation or reason to modify compound 12 because Barden describes the desirability of extending the alkyl chain of the *N*-alkylglycinamide group in tetracycline compounds substituted at the 9-position. The Examiner concluded that one of ordinary skill would expect the desirability of extending the alkyl moiety to equally apply to 9-carbamate substituted tetracyclines, particularly in view of Silverman. (*See* Office Action at pp. 3-4).

Applicants have canceled claim 66 and previously canceled claim 18. Therefore, with respect to these claims, the rejection is moot. With respect to claims 1, 7, 11, 23-25 and 67, Applicants traverse the rejection.

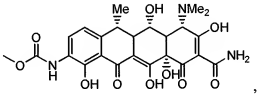
Barden's compound 12 exhibits no antibacterial activity against gram negative bacteria (*i.e.*, *E. coli* strains). However, the currently claimed compounds are effective against both gram positive and gram negative bacteria, and therefore, possess superior properties and not similar properties (*see* data showing antibacterial activity against both gram positive and gram negative bacteria at *e.g.*, Example 2 and Table 2 of the specification as filed).

In 2008, the Federal Circuit revisited the issue of obviousness in the context of chemical compounds in *Eisai Inc. v. Dr. Reddy's Laboratories, Inc. and Teva Pharmaceuticals USA, Inc* (Fed. Cir. 2008). The Court stated

> Where, as here, the patent at issue claims a chemical compound, the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1377 (Fed. Cir. 2006) (noting that, for a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter...where the prior art gives reason or motivation to make the claimed compositions" (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc))). Obviousness based on structural similarity thus can be proved by identification of some motivation that would have lead one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound. *See Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). In keeping with the flexible nature of the obviousness inquiry, *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), the requisite motivation can come from any number of sources and need not necessarily be explicit in the art. *See Aventis Pharma Deutschland GmbH v. Lupin,*

Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007). Rather "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship…to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id.* (quoting *Dillon*, 919 F.2d at 692).

The pending claims are drawn to 7- or 9-carbamate substituted tetracycline compounds. Specifically, independent claim 1 is drawn to substituted tetracycline where R^9 is hydrogen or $NR^{9c}C(=Z')ZR^{9a}$. The remaining claims subject to this rejection depend, directly or indirectly, from this claim. The Examiner cites Barden's compound 12 as relevant:



where ZR^{9a} is methoxy (*i.e.*, R^{9a} is methyl). Compound 12 is one of 15 compounds described in Table 1, and one of more than 40 compounds specifically described in Barden. The Examiner does not cite any other compounds as relevant.

The Examiner stated that compound 12 has greater activity in some respects than other compounds described by Barden and, thus, one of ordinary skill would have had sufficient motivation to select compound 12 for further modification. (*See* Office Action at p. 3). However, even if this were true, Applicants have shown that the claimed 9-carbamate substituted tetracycline compounds are effective against both gram positive and gram negative bacteria (*see e.g.*, Example 2 and Table 2 of the instant specification). Specifically, 9-alkylcarbamate substituted compounds M, AA, AP, AS, BQ, BR and BV exhibit activity against several bacterial strains, including a gram negative bacterium, *E. coli*. Barden describes compound 12 as only being active against gram positive species (*i.e.*, *S. aureus* strains) and not gram negative strains as exemplified by lack of activity against *E. coli* (*see* Barden, Table 1 and p. 3206, right column, lines 28-33). Thus, the claimed compounds have superior properties, and not similar properties, relative to compound 12.

Furthermore, Barden does not provide sufficient motivation or any objective reason to select and/or modify compound 12, a 9-carbamate substituted doxycycline derivative, to arrive at the currently claimed compounds. Rather, Barden describes 9-glycylamido-substituted doxycycline derivatives throughout the reference. Barden's discussion of the data presented in Table 1 concludes with a statement of the superior properties exhibited by *N,N*-

dialkylglycinamide compounds, not carbamates: "*N,N*-dialkylglycinamides exhibited maximal activity, and that activity was retained by a variety of nitrogen substituents." (*See* Barden at p. 3207, left column, lines 2-4). Moreover, Barden's discussion of Table 1 fails to even mention compound 12.

Following Table 1, Barden describes the use of amino acids in further studies of *N*-alkyl and *N,N*-dialkylglycinamides rather than any discussion of either compound 12 or 9-carbamate substituted tetracycline compounds in general. (*See* Barden at page 3207, left column, line 5 through right column, line 4). Various amino acid-substituted 9-glycylamido doxycycline derivatives, and no carbamates, are included in Table 2. (*See* Barden at page 3208, Table 2). Therefore, Barden describes the use of substituted 9-glycinamide tetracycline compounds, and not the currently claimed 9-carbamate substituted tetracycline compounds, for the treatment of infection.

In view of the above, one of ordinary skill would not have selected compound 12 as a candidate for further modification and/or study. Thus, it would not have been obvious to single out the particular compound (compound 12) identified by the Examiner, let alone to select this compound for use in the treatment of a tetracycline responsive state.

In addition, Barden does not provide sufficient motivation or any objective reason to modify compound 12 to arrive at the claimed invention. Barden teaches that lengthening the alkyl chain of the *N*-alkylglycinamide group at the 9-position results in increased potency of the described tetracycline compounds (compounds 17, 18 and 21 in Table 1). None of these compounds include a 9-carbamate substituted tetracycline structure. Moreover, Table 1 does not include sufficient data to draw a comparative conclusion with respect to 9-carbamate tetracyclines, as only one 9-carbamate tetracycline structure (compound 12) is described.

Silverman does not cure the deficiencies of Barden. The Examiner cites Silverman as evidence that homologation of alkyl chains can lead to improved chemical properties. (*See* Office Action at p. 4). However, according to Silverman, lengthening a carbon chain can also decrease potency due to increased lipophilicity or the formation of micelles. (*See* Silverman at page 16 and Table 2.1 on page 17). Silverman also teaches a generic description of homologation of a substituted resorcinol and a mandelic acid ester, yet there is no indication that the same principle holds true for 9-carbamate substituted tetracycline compounds. The currently claimed 9-carbamate substituted tetracycline compounds are chemically unrelated to the single-ring aromatic compounds described in Silverman. As a

result, one of ordinary skill would not have reasonably expected that the claimed 9-carbamate substituted tetracycline compounds would result in improved properties.

Thus, in view of Silverman, it would not have been obvious to single out the particular compound (compound 12) identified by the Examiner, or to choose lengthening of the R^{9a} carbon chain as a preferred or otherwise desirable means for modifying this compound.

As described above, Barden fails to provide any motivation or objective reason to select and/or modify compound 12. Further, Silverman provides no motivation or objective reason to select and/or modify compound 12 to arrive at the claimed invention. Thus, Applicants submit that the combination of Barden and Silverman does not render claims 1, 7, 11, 23-25 and 67 obvious. Applicants request reconsideration and withdrawal of the rejection.

35 U.S.C. §112

Claims 1-4, 6, 7, 9-13, 19, 21, 23, 24, 32 and 82 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

Claims 1 and 82 have been amended to further define the invention.

Applicants have canceled claim 12. Therefore, with respect to this claim, the rejection is moot. With respect to claims 1-4, 6, 7, 9-11, 13, 19, 21, 23, 24, 32 and 82, Applicants traverse the rejection.

The Examiner stated that claims 1, 32 and 82 create unsupported new subgenera. Specifically, according to the Examiner, claims 1 and 82 recite an unsubstituted C_3-C_{10} alkyl group for R^{9a} which lacks sufficient support in the original disclosure. (*See* Office Action at pp. 4-5). Also, the Examiner asserted that previously amended claim 32 describes a subgenus which was not specifically recited.

Claims 1 and 82 Scope of R^{9a}

The current scope of R^{9a} is supported by the original disclosure. Applicants herein amend claims 1 and 82 to include "t-butyl, n-butyl, i-butyl and n-pentyl" in the definition of R^{9a}. Support for this amendment can be found, *e.g.*, on page 6, lines 23-24 of the specification as filed.

Furthermore, claims 1 and 82 have been amended (*e.g.*, variables X, R^2, $R^{2'}$, R^3, R^4, $R^{4'}$, R^5, R^6, $R^{6'}$, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{9a}, R^{9c}, R^{10}, R^{11} and R^{12}) to further define the invention. In particular, R^{9a} is defined as: t-butyl, n-butyl, i-butyl, n-pentyl, substituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted alkoxy, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted arylcarbonyl, or substituted or unsubstituted phenyl. The full scope of R^{9a} is supported by the specification and claims as originally filed. For example, compounds F, M, AS, BR and BV of Table 2 comprise t-butyl, n-butyl, i-butyl or n-pentyl R^{9a} groups, compounds A, Y and AN of Table 2 comprise a substituted alkyl R^{9a} group, compounds Z, AM, AQ, BJ and BT of Table 2 comprise substituted or unsubstituted alkenyl R^{9a} groups, compounds X and AH of Table 2 comprise substituted or unsubstituted arylsulfonyl R^{9a} groups, compound AT of Table 2 comprises a substituted alkoxycarbonyl R^{9a} group, compounds BE and BF of Table 2 comprise substituted or unsubstituted alkoxy R^{9a} groups, compound BG of Table 2 comprises an unsubstituted arylcarbonyl R^{9a} group and compounds B, D, E, I, K, L, AB, AC, AD, AE, AF, AG, AI, AJ, BB, BC, BD, BE, BF, BH, BI, BK, BL, BM, BN, BO, BP and BU of Table 2 comprise substituted or unsubstituted aryl R^{9a} groups. Additional groups, such as alkynyl, are also described throughout the specification and claims as originally filed. (*See e.g.*, page 14, line 2 through page 17, line 20).

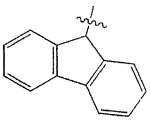
Moreover, synthetic scheme 1 describes a synthetic pathway to make the claimed compounds. Thus, Applicants submit that the specification describes the currently amended claims in sufficient detail such that a skilled artisan would conclude that Applicants had possession of the claimed invention at the time the application was filed. Applicants request reconsideration and withdrawal of the rejection.

Claim 32

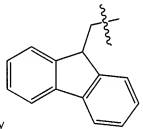
Chapter 2163.02 describes the standard for complying with the written description requirement.

> Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures,

diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed.Cir.1997).



Applicants previously amended claim 32 to remove the moiety ,



replaced it with the moiety and specified that the moiety is a substituted alkyl group. Support for this claim can be found, *e.g.,* on page 6, line 23 through page 7, line 9, where the specification states R^{9a} can be substituted alkyl (such as substituted methyl) and lists aryl (such as fluorene) as a possible substituent. Specifically, the specification states "[i]n one embodiment, R^{9a} is substituted or unsubstituted alkyl (e.g., methyl, ethyl, t-butyl, n-butyl, i-butyl, or n-pentyl.) Examples of possible substituents include but are not limited to...aryl" (*see* p. 6, line 23 through p. 7, line 8 of the specification as filed). In addition, the next paragraph of the specification describes a further embodiment where R^{9a} includes at least one aryl group and specifically mentions fluorene as an aryl group included in the R^{9a} substituent (*see* p. 7, lines 11-13 of the specification as filed). Finally, several species described in the specification include fluorene as an aryl group in the R^{9a} substituent (*see e.g.*, p. 10, lines 12 and 17 and compounds A and AT from Table 2). These specific descriptions demonstrate possession of the invention by the Applicants at the time the application was filed.

Applicants submit that the specification describes the claimed invention in sufficient detail such that a skilled artisan would conclude that Applicants had possession of the claimed invention at the time the application was filed. Applicants request reconsideration and withdrawal of the rejection.

Claims 1-4, 6, 7, 9-13, 19, 21, 23, 24, 32 and 82 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

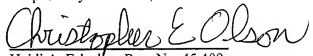
The Examiner stated that claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the claims use definitions for variables including a "prodrug moiety." (*See* Office Action at pp. 6-7).

Applicants have canceled claim 12. Therefore, with respect to this claim, the rejection is moot. With respect to claims 1-4, 6, 7, 9-11, 13, 19, 21, 23, 24, 32 and 82, Applicants traverse the rejection. However, in an effort to further prosecution, Applicants have herein amended claims 1 and 82. The remaining claims currently under this rejection (*i.e.*, claims 2-4, 6, 7, 9-13, 19, 21, 23, 24 and 32) are directly or indirectly dependent upon claim 1, and thus, incorporate the limitations of claim 1. Applicants submit that amended claims 1 and 82 overcome this rejection and reconsideration and withdrawal of the rejection is requested.

CONCLUSION

Applicants respectfully submit that this application is in condition for allowance. If there are any questions regarding this amendment and/or these remarks, the Examiner is respectfully requested to telephone the Applicants' attorney/agent undersigned.

Respectfully submitted,



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Date: August 18, 2009